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EXAMINER

QIAN, CELINE X

ART UNIT PAPER NUMBER

1636

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/661,804

Applicant(s)

SCHULER ET AL.

Examiner

Celine X. Qian Ph.D.

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 12 and 24-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 12 and 24-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                                            |                                                                                         |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                           | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

### **DETAILED ACTION**

Claims 12, 24-32 are pending in the application.

This Office Action is in response to the Amendment filed on 9/6/06.

#### ***Response to Amendment***

Acknowledgement is made of Applicant's submission of foreign priority document.

The amendment to the specification has been entered.

The rejection of claims 12, 24-27 under 35 U.S.C. 112 2<sup>nd</sup> paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 12, 24-27 and newly added claims 28-30 under 35 U.S.C. 102 is maintained for reasons set forth of the record mailed on 5/5/06 and further discussed below.

Claims 31 and 32 is rejected under 35 U.S.C. 103 (a) for reasons discussed below.

#### ***Response to Arguments***

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 12, 24-29 rejected under 35 U.S.C. 102(a) as being anticipated by Jonuleit et al.

This rejection is rewritten below to address the current amendment and addition of new claims.

Jonuleit et al. disclose a method that of identify, monitor and/or remove CD4+CD25+ cells from human blood by contacting the blood with CD4 and/or CD25 and/or CTL-A4 specific antibodies (see page 1214, 2<sup>nd</sup> col., 4<sup>th</sup> paragraph, lines 1-6, and Figure 4). Jonuleit et al. further

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disclose that CD4<sup>+</sup> T cells are removed from the cord blood (page 1214, 2<sup>nd</sup> col., 4<sup>th</sup> paragraph, lines 1-3). Jonuleit et al. also disclose that the purification is carried out using antibodies attached to beads (page 1214, 2<sup>nd</sup> col., 4<sup>th</sup> paragraph, last two lines). Lastly, Jonuleit et al. disclose said method wherein the cells are stimulated with dendritic cells (see page 1215, 1<sup>st</sup> paragraph, lines 2-4). Further, Jonuleit et al. disclose analyzing expression of CTL-4. Therefore, Jonuleit et al. disclose the instantly claimed invention.

In response to this rejection, Applicants argue that the population described by Jonuleit et al. is not a naturally occurring population. Applicants argue Jonuleit et al. teach the production of cells having the specified properties rather than identifying, monitoring and/or removing of a natural population from human blood as claimed. Furthermore, Applicants argue that Jonuleit et al. does not teach that CD4<sup>+</sup> T cells removed from blood have regulatory properties. Applicants thus conclude that the claimed invention is not anticipated by this reference.

The above argument have been fully considered but deemed unpersuasive. Although the claimed method has the preamble of identifying, monitoring and/or removing CD4<sup>+</sup>CD25<sup>+</sup> cells from human blood, the active method step is simply contacting the human blood with ligands specifically binds to the CD4 and CD25, and/or CTL-A4. Jonuleit et al. teach this method step (see Figure 4). The instant claim recites human blood, which is not limited to “natural population from human blood.” The CD4<sup>+</sup> cells taught in Jonuleit et al. are purified from human cord blood (see page 1214, 4<sup>th</sup> paragraph), thus, it meets the limitation of the instant claims. Moreover, newly added claims 28 and 29 are directed claimed method with an additional step of testing a regulator property such as constitutive expression of CTLA-4, this step is disclosed in

this reference too (see page 1216, 1<sup>st</sup> col., 2<sup>nd</sup> paragraph, lines 7-17). Therefore, for reasons set forth in the previous office action and above, this rejection is maintained.

Claims 12, 24-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Horwitz (US 6,803,036). This rejection is rewritten below to address the current amendment and addition of new claims.

Horwitz et al. disclose a method that of identify, monitor and/or remove CD4+CD25+ cells from human blood by contacting the blood with CD4 and/or CD25 and/or CTL-A4 specific antibodies (see for example Figure 9 and 10A, and col. 7, lines 49-65, and col. 21, lines 60-67). Horwitz et al. further disclose that CD4+ T cells are removed from the cord blood (col. 7, lines 8-12). Horwitz et al. also disclose that the purification can be carried out using antibodies attached to solid support (col. 11, lines 60-65). Further, Horwitz et al. disclose said method wherein the cells are stimulated (see col.23, lines 6-12). Moreover, Horwitz et al. disclose the CD4+CD25+ cells showed suppressive activity when cocultured with CD4+ or CD8+ cells (see col. 22, 1-4<sup>th</sup> paragraph), in a contact dependent fashion (see col. 21, 4<sup>th</sup> paragraph). Therefore, Horwitz et al. disclose the instantly claimed invention.

In response to this rejection, Applicants argue that Horwitz et al. teach the induction of regulatory T cells from CD4+ T cells by stimulation with TGF- $\beta$ . The population described by Horwitz et al. is not a naturally occurring population. Applicants further assert that it is not clear whether Horwitz demonstrates the use of human cells because the word human is only used a few times in the specification, wherein the most examples describe the use of cells from patients, a term includes rodents. Furthermore, Applicants argue that Horwitz et al. does not teach that

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CD4+ T cells removed from blood have regulatory properties. Applicants thus conclude that the claimed invention is not anticipated by this reference.

The above argument have been fully considered but deemed unpersuasive. Although the claimed method has the preamble of identifying, monitoring and/or removing CD4+CD25+ cells from human blood, the active method step is simply contacting the human blood with ligands specifically binds to the CD4 and CD25, and/or CTL-A4. Horwitz et al. teach this method step (see for example Figure 9 and 10A, and col. 7, lines 49-65, and col. 21, lines 60-67). The instant claim recites human blood, which is not limited to "natural population from human blood." The CD4+ cells taught in Horwitz et al. are purified from human blood (see example 7, lines 64-66). Contrary to Applicant's assertion, the cells disclosed in the examples are all from human rather than rodent origin because they are collected from donor A or B. In col. 6, lines 61-63, it discloses that donor A is a human. As such, the cells disclose in this reference satisfies the claim limitation. With regard to Applicants' argument of newly added claims, it is reminded that T cell population with CD4+CD25+ expression marker would have same regulatory properties (function) regardless how it is obtained. Since the claims are directed to methods having steps of contacting human blood cells with ligands that binds CD4+ and CD25+ surface marker, and an additional step of analyzing a property of regulatory function, whereas Horwitz et al. disclose both steps, this reference clearly anticipates the instantly claimed invention. Therefore, for reasons set forth in the previous office action and above, this rejection is maintained.

***New Grounds of Rejection Necessitated by Applicant's Amendment***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al.

The teaching of Horwitz et al. is discussed above. Horwitz et al. teach that CD4+CD25+ cells are activated (see example 7). However, Horwitz et al. do not teach that the CD4+CD25+ cells are activated and fixed.

It would have been obvious to one of ordinary skill in the art to use such population of cells which is activated and fixed. It is well known in the art that cells need to be fixed for the purpose of observing properties under microscope. One of ordinary skill in the art would have been motivated to use the fixed activated CD4+CD25+ cells to test its regulatory activity because said cells may be looked at under the microscope. The level of skill in the art is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation of success to fix the activated cell and test its regulatory activity. Therefore, the claimed invention would have been *prima facie* obvious at the time the invention was made.

Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al., in view of Jonuleit et al.

The teaching of Horwitz et al. was discussed above. However, Horwitz et al. do not teach analyzing the CD4+CD25+ cells for a cytokine profile of predominant secretion of IL-10 and only low levels of IL-2, IL-4 and IFN- $\gamma$ .

Jonuleit et al. teach enhanced production of IL-10 and low production of IL-2, IL-4 and IFN- $\gamma$  is a characteristic of Tr1 cells (see page 1216, 2<sup>nd</sup> col., lines 5-10).

It would have been obvious to one of ordinary skill in the art to test the cytokine profile of predominant secretion of IL-10 and only low levels of IL-2, IL-4 and IFN- $\gamma$  of the CD4+CD25+ cells taught by Horwitz et al. because it is a characteristic of Tr1 cells. Horwitz et al. has demonstrated that the CD4+CD25+ cells from human blood has regulatory activity such as suppression of T cell activation, it would have been obvious to further characterize whether this population has the Tr1 cell characteristic such as predominant secretion of IL-10 and only low levels of IL-2, IL-4 and IFN- $\gamma$ . One of ordinary skilled in the art would have been motivated to do so to analyze the property of said population completely and determine whether it can be used for clinical treatment. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to determine the cytokine profile of the CD4+CD25+ cells. Therefore, the claimed invention would have been *prima facie* obvious at the time the invention was made.



***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.  
Examiner  
Art Unit 1636

CELINE QIAN, PH.D.  
PRIMARY EXAMINER

